CASE REPORT

Osteoporosis and malignancy: a dicey combination

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SUMMARY

Osteoporosis is the most common metabolic bone disorder worldwide, especially in women. Postmenopausal status is the most common risk factor for osteoporosis in elderly women. The operational diagnosis of osteoporosis is usually made with the help of central dual energy X-ray absorptiometry scan. Clinically, osteoporosis is suspected in the background of one or more fractures of the hip, vertebra, proximal humerus or pelvis in the absence of local disease or high-energy trauma. Serious underlying illness can present with vertebral fractures and can be missed if other clues from clinical examination and investigations are overlooked. We report a case emphasising this aspect.

BACKGROUND

A secondary cause is found in up to 30% of postmenopausal women presenting with fracture and osteoporosis.¹ A minority of them have serious and potentially treatable conditions. It is important to identify such conditions to avoid devastating complications and to ensure appropriate treatment.

CASE PRESENTATION

A 52-year-old postmenopausal woman presented with a history of a low backache for 4 months. X-ray of the lumbosacral spine revealed a central partial compression collapse of the L1 vertebral body (figure 1). Dual energy X-ray absorptiometry (DXA) scan concomitantly showed unequivocal evidence of osteoporosis. She was referred to the department of endocrinology for management of postmenopausal osteoporosis.

The pain had started insidiously and worsened significantly, limiting her day-to-day activities. There was no history of trauma. She had a history of occasional cough with minimal mucoid white sputum production for 2 months. She did not have any difficulty in breathing, fever, changes in appetite or weight loss or haemoptysis. She was not known to have renal calculi or any other chronic medical illness. She was not on any long-term medication or corticosteroids. She had attained menopause 10 years back and was not on any calcium or vitamin D supplements. Her dietary calcium intake was approximately 500 mg per day. Her medical history and family history were otherwise insignificant.

On examination, she was in considerable pain. She had tenderness over the L1 vertebra. General physical examination and other systemic examination were unremarkable. There were no bony deformities.

INVESTIGATIONS

Baseline investigations like complete haemogram, liver and renal function tests were normal. A fasting blood sample showed mild hypercalcaemia (corrected serum calcium of 10.6 and 11.3 mg/dL on two occasions; normal 8–10) and normal serum phosphorus level (3.8 mg/dL; normal 2.5–4.5). Serum alkaline phosphatase was elevated five times above the normal upper limit (1412 IU/L; normal—up to 220 IU/L). Her serum 25-OH vitamin D was 9 ng/mL (normal 20–100) and intact parathyroid hormone (PTH) was 40.7 pg/mL (normal 10–65). Thyroid function test and arterial blood gas analysis were normal. DXA scan was suggestive of osteoporosis of the lumbar spine (L2–L4) with a T score of –4.1 and osteopenia at the distal radius and neck of femur with T scores of –2.2 and –1.9, respectively. Her thin body frame (weight 38 kg, BMI 16.8 kg/m²), insufficient calcium intake, vitamin D deficiency and immobility due to debilitating backache could have contributed to the low bone mass.

The presence of hypercalcaemia and markedly elevated alkaline phosphatase level pointed to a potential secondary aetiology. Serum electrophoresis and urine for Bence Jones protein were normal. Tumour markers, CA-125 (102.4 U/mL; normal 0–35 U/mL) and Carcinoembryonic antigen (CEA) (50.9; normal 0–3 ng/mL) were elevated. A fracture of the L1 vertebra with preservation of disc space was detected on the X-ray of the spine. Skeletal imaging also revealed multiple lytic lesions in the right humerus and skull. Bone scan showed additional foci of uptake in bilateral scapulae, multiple ribs, sternum, multiple vertebrae, pelvis, bilateral femur and bilateral tibiae, suggestive of extensive osteoblastic metastatic lesions (figure 2). Chest X-ray revealed a soft tissue density in the right lower lung field. Contrast-enhanced CT (CECT) of the neck, chest and abdomen revealed scattered ground glass opacities in both lung fields secondary to pulmonary embolism and a spiculated nodule in the lower lobe of the right lung, suspicious of malignancy (figure 3). Multiple expansile lytic bony lesions involving the spine, pelvic bones and sternum were also evident (figure 4). No suspicious parathyroid lesion was detected in the CECT neck. Left common iliac vein thrombosis was also noted.

DIFFERENTIAL DIAGNOSIS

Certain unusual factors in the presentation of this patient pointed to a much serious underlying pathology. First, the severity of bone pain and

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Figure 1 X-ray of the lumbosacral spine showing central partial compression collapse of L1 vertebral body with preserved disc space.

functional disability were disproportionate to that expected in a case of osteoporotic vertebral fracture. Although the patient was 10 years postmenopausal and had a history of poor dietary calcium intake, other traditional risk factors for sustaining a fracture were absent. This prompted a search for other aetiologies in this patient. Although clinical examination was unrevealing, derangements of laboratory parameters like hypercalcaemia and markedly elevated alkaline phosphatase levels confirmed the suspicion of a secondary aetiology. Serum intact PTH was, however, inappropriately normal in the face of hypercalcaemia indicating a PTH-driven process. Primary hyperparathyroidism and vitamin D deficiency-triggered secondary hyperparathyroidism were considered as possibilities. Meanwhile, the chest X-ray revealed a suspicious-looking lesion in the right lung. CT chest revealed a nodule with a high probability of malignancy. Incidentally, multiple bony lytic expansile lesions were noted in the humerus, skull and osteoblastic lesions on skeletal survey, suggesting the possibility of metastatic bone lesions. Bone marrow examination showed metastatic deposits of adenocarcinoma.

TREATMENT

Hypercalcaemia responded to rehydration and intravenous zoledronic acid. Vitamin D replacement therapy was initiated at a dose of 2000 IU/day to correct the deficiency and prevent hypocalcaemia following intravenous bisphosphonate administration. Pain relief was achieved with opioids and calcitonin. Oncology consultation was sought and in view of the

Figure 2 Bone scan showing multiple foci of uptake in the skull, humeri, bilateral scapulae, multiple ribs, sternum, multiple vertebrae, pelvis, bilateral femur and bilateral tibiae, suggestive of extensive osteoblastic metastatic lesions.

extent of the disease, she was advised palliative care and oral gemcitabine.

OUTCOME AND FOLLOW-UP

The nature and extent of the disease, its prognosis and treatment options were explained to the patient and her kin. The

Figure 3 A 2.2x1.3 cm heterogeneously enhancing spiculated mass is seen in the lower lobe of the right lung. Bilateral pleural effusion is also noted.

Figure 4 Coronal and sagittal reformats in bone window showing multiple expansile lytic bony lesions involving the spine, pelvic bones and sternum.

patient was discharged at the behest of her relatives and was subsequently lost to follow-up.

DISCUSSION

Skeletal metastasis is commonly encountered in malignancies of the breast and prostate.² Around 30%–40% of patients with primary lung malignancy have secondary cancerous deposits in the skeleton. The vertebrae show a remarkable predilection for metastasis although pathological fractures commonly involve the long bones.³

Hypercalcaemia is often incidentally detected and since the clinical features can be subtle and non-specific, a high index of suspicion is necessary.⁴ In an apparently well patient in an outpatient setting, hypercalcaemia is most often due to primary hyperparathyroidism and other benign disorders. Paraneoplastic hypercalcaemia is the most common cause of hypercalcaemia in hospitalised patients.⁵ The first logical step in the evaluation of hypercalcaemia is the measurement of serum PTH levels. Inappropriately normal or elevated PTH level indicates a primary PTH-driven process, the most common aetiology being a parathyroid adenoma.⁶ Tertiary hyperparathyroidism can result in hypercalcaemia in patients with advanced renal failure. Other rare PTH-mediated causes include familial hypocalciuric hypercalcaemia and lithium-induced hypercalcaemia.⁵ Among patients with malignancy, hypercalcaemia most often results from excessive secretion of Parathyroid hormone-related protein (PTHrP) by the tumour cells (humoral hypercalcaemia of malignancy). In the remaining, local osteolysis by the secretory products of the cancerous cells is the prime factor.⁷ Few cases of lymphomas secreting 1,25 hydroxyvitamin D have been reported.⁸ In all these instances, PTH is appropriately suppressed as a result of negative feedback inhibition. Ectopic secretion of PTH has been rarely reported in patients with malignancy.⁹ Other causes of PTH-independent hypercalcaemia include granulomatous disorders with unregulated production of 1,25 hydroxyvitamin D, other endocrine disorders like hyperthyroidism and adrenal insufficiency and drugs like thiazides, excess of vitamin D and A.⁴

In our patient, unsuppressed PTH could be attributed to secondary hyperparathyroidism due to vitamin D deficiency but it remained so following correction of vitamin D deficiency (repeat vitamin D levels 21 ng/mL). So, the possibility of primary hyperparathyroidism was still considered. CT scan of the neck did not show any evidence of a parathyroid adenoma. However, the sensitivity of a CT scan to pick up an adenoma is only 50%–70%.¹⁰ Further investigations like ultrasound and sestamibi scintigraphy

were planned, but unfortunately, could not be done due to the untimely discharge of the patient.

Severe (corrected serum calcium >14 mg/dL) and symptomatic hypercalcaemia needs prompt treatment.¹¹ Isotonic saline infusion corrects dehydration resulting from polyuria and vomiting. It also promotes urinary calcium excretion similar to loop diuretics by reducing tubular reabsorption of sodium and calcium.¹² Calcitonin inhibits resorption of bone and also promotes excretion of calcium. Intramuscular or subcutaneous administration of calcitonin results in rapid reduction of calcium levels within 2–6 hours of administration. However, its utility is limited by development of tachyphylaxis after 24–48 hours due to downregulation of the calcitonin receptors on osteoclasts.¹³ Intravenous bisphosphonates (zoledronic acid or pamidronate) and denosumab are potent inhibitors of bone resorption. The effect of these drugs is usually seen after 3 days of administration and can cause prolonged suppression of calcium levels. Calcitonin is often combined with bisphosphonates or denosumab as a bridge therapy. Denosumab is preferred in patients with impaired renal function in whom bisphosphonates are contra-indicated.¹⁴ Glucocorticoids inhibit the production of 1,25 hydroxyvitamin D and are helpful in patients with granulomatous disorders, vitamin D toxicity and lymphoma.¹⁵ Dialysis is effective in concomitant renal failure limiting other treatment options or in refractory cases.

Learning points

- ▶ Osteoporosis can be clinically diagnosed on the findings of one or more vertebral compression fractures in the absence of local disease or high-energy trauma and operationally confirmed with central dual energy X-ray absorptiometry scan.
- ▶ A search for additional risk factors and secondary aetiology for osteoporosis should be initiated when there are atypical presenting features.
- ▶ Hypercalcaemia with pathological fractures is either due to hyperparathyroidism or skeletal involvement due to malignancy.

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